THE AMENDMENTS

In the Claims:

1. (Currently Amended) An oligonucleotide conjugate comprising:

(a) an oligonucleotide at least part of whose sequence is complementary to an intracellular nucleic acid sequence; and

(b) a somatostatin analog,

wherein the somatostatin analog is covalently bonded to a base present in the oligonucleotide molecule via a spacer.

2. (Original) The oligonucleotide conjugate according to claim 1, wherein the oligonucleotide is an oligodeoxyribonucleotide.

3. (Original) The oligonucleotide conjugate according to claim 1 or 2, wherein the phosphodiester compounds in the oligonucleotide are partially or fully replaced by phosphorothioate compounds.

4. (Previously Presented) The oligonucleotide conjugate according to claim 1, wherein the 3' end in the oligonucleotide is covalently bonded to a propanediol group.

5. (Previously Presented) The oligonucleotide conjugate according to claim 1, wherein the somatostatin analog is octreotide or octreotate, or a derivative thereof.

6. (Previously Presented) The oligonucleotide conjugate according to claim 1, wherein the somatostatin analog is covalently bonded to the 5'end of the oligonucleotide molecule.

7. (Cancelled)

8. (Previously presented) The oligonucleotide conjugate according to claim 5 or 6, wherein the somatostatin derivative is Tyr^3 octreotate.

9. (Previously Presented) The oligonucleotide conjugate according to claim 1, wherein the intracellular nucleic acid sequence is an mRNA or viral RNA.

10. (Original) The oligonucleotide conjugate according to claim 9, wherein the intracellular nucleic acid sequence is the coding portion of an mRNA.

11. (Previously Presented) The oligonucleotide conjugate according to claim 1, wherein the oligonucleotide has a length of 8 to 50 nucleotides.

12. (Original) The oligonucleotide conjugate according to claim 11, wherein the oligonucleotide has a length of 12 to 20 nucleotides.

13. (Previously Presented) The oligonucleotide conjugate according to claim 1, wherein the oligonucleotide is partially complementary to the nucleic acid coding for the proto-oncogene bcl-2.

14. (Withdrawn) The oligonucleotide conjugate according to claim 13, which comprises the nucleic acid sequence of SEQ ID NO:1.

15. (Currently Amended) The oligonucleotide conjugate according to claim 1, wherein the oligonucleotide is a peptide nucleic acid derivative ~~(PNA)~~.

16-18. (Cancelled.)

The Amendments

Claim 1 has been re-written and amended to reflect the Examiner's findings in the Advisory Action regarding the denial of entry of proposed amendments in Applicant's Office Action Response dated September 22, 2003. The amendment to Claim 1 has support in cancelled Claim 7, and therefore is within the scope of the claims already searched. Claims 16-18 have been cancelled.

No new matter is added in these amendments. The Examiner is respectfully requested to enter the amendments.

The Remarks

35 U.S.C. § 112 Rejection

Claims 16-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. This rejection is rendered moot in light of the amendments.

Applicants have canceled claims 16-18 without prejudice. The cancellation of claims 16-18 were made in order to place the application in a more favorable form for allowance. Therefore, the §112 rejection is rendered moot, and should be withdrawn.

35 U.S.C. § 103(a) Rejection – Claims 1-3

Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of references of Nagy et al., in view of Lu et al. and Taylor et al. This rejection is overcome in part in view of the amendments and in part in view of the remarks below.

The Examiner asserts that it would have been allegedly obvious for one of ordinary skill in the art to substitute an antisense compound as taught by Lu et al. in place of the cytotoxic compound of the somatostatin analog conjugates as taught by Nagy et al., as well as to incorporate phosphorothioate modifications into the antisense molecules of Lu et al. because Taylor et al. allegedly teach that such modifications improve bioactivity half-life and cellular uptake of antisense molecules.

In order to make a showing of obviousness under 35 U.S.C. § 103(a), the Examiner must consider the claimed invention as a whole; 2) the references "must suggest the desireability and thus the obviousness of making the combination"; 3) the Examiner cannot view the references using the benefit of "impermissible hindsight vision"; and 4) the Examiner must apply "a reasonable expectation of success" standard when viewing the application. MPEP § 2141 "35 U.S.C. 103; the Graham Factual Inquiries". When considering the claimed invention as a whole, a proper combination of references must first and foremost comprise all of the elements of the instant invention.

In view of these requirements, the Examiners' assertions respectfully do not comport with the requirements of a prima facie case of obviousness showing under 35 U.S.C. § 103(a). Even if the combination of the references were considered proper, which the Applicants refute below, the combination of the alleged prior art references do not disclose all of the elements of the claimed invention. The present invention is directed to an oligonucleotide conjugate comprising an oligonucleotide and a somatostatin analog, wherein the somatostatin analog is covalently conjugated to the oligonucleotide at the 5'end of said oligonucleotide. Example 4 shows how the oligonucleotide conjugate is synthesized. Figures 1 and 3 show the chemical structure of the oligonucleotide-somatostatin conjugate. The oligonucleotide is conjugated to a somatostatin analog by reacting a phosphorothioate compound (containing the oligonucleotide) with the maleimido peptide (somatostatin analog). The invention is illustrated with the oligonucleotide/somatostatin conjugate having a stable thioether bond.

Nagy et al. discloses a doxorubicin/somatostatin conjugate. In contrast to the stable thioether bond of the present invention, the 2-pyrrolino-DOX-14-O-hemiglutarate of Nagy et al. is linked to the amino terminus of a somatostatin analogue and forms a peptide bond. One of ordinary skill in the art would know that such a peptide linkage does not work for linking an oligonucleotide to a somatostatin analogue. There is no teaching or suggestion in Nagy et al. regarding an oligonucleotide/somatostatin conjugate. Moreover, Nagy et al. fails to teach a practitioner how to prepare such a conjugate, which is essential because the structures of an oligonucleotide and doxorubicin are completely different. Furthermore, the functional moiety of an oligonucleotide that is used for preparing a covalent conjugate is different from that of

doxorubicin. A skilled person cannot extrapolate from a doxorubicin conjugate to an oligonucleotide conjugate.

Adding Lu et al. or Taylor et al. does not cure the deficiencies of Nagy et al. Lu et al. teach a non-covalent means of coupling an oligonucleotide to asialoglycoprotein. Not only does Lu et al. teach a different carrier protein, but it teaches a functionally and structurally different means of coupling the oligonucleotide to the carrier. One of ordinary skill in the art would not know from the teachings of Lu et al. how to couple oligonucleotides to the carrier protein to make the claimed invention. Therefore, even if the combination of the references were proper, which the Applicants refute below, they do not disclose all of the elements of the claimed invention because they do not teach the composition of somatostatin covalently conjugated to an oligonucleotide. The Examiners' assertions fail to prove a prima facie case of obviousness.

In addition, the combination of references are improper because it does not teach or suggest the desireability, and thus the obviousness of making the combination. Specifically, neither Nagy et al., nor Lu et al. or Taylor et al. suggest or teach the desireability of combining somatostatin analogs covalently coupled to antisense oligonucleotides. Lu et al. does not teach or suggest a means of substituting a covalently-bound peptide hormone as a carrier for the antisense oligonucleotides, as is now recited in the amended claims. In fact, Lu et al., through the teachings of Wu et al., teaches away from the instant invention because Wu et al. teaches that "covalent coupling might alter the DNA and preclude proper gene expression." *See* Wu, G.Y., Wu, C.H., "Receptor-mediated in vitro gene transformation by a soluble DNA carrier system" J. Biol. Chem. 262:4429 (1987), at 4429, right column, lines 14-16, reference provided herein. In fact, subsequent prior art references of Wu et al., which Lu et al. depends upon for its teachings, consistently use a non-covalent means of binding DNA through non-covalent interactions with poly-L lysine, teaching that the non-covalent means is nondamaging as compared to a covalent means of coupling. *See* Wu et al., J. Biol Chem. Vol. 263 at 14621 (1988), 2nd column, lines 3-4 ("poly-L-lysine that can bind DNA in a *noncovalent and nondamaging interaction*") (emphasis added); and Wu et al., J. Biol. Chem. Vol. 266 at 14338 (1991), 2nd col., lines 2-3 ("(e.g. poly-L-lysine) that can bind DNA in a *nondamaging* electrostatic interaction") (emphasis added), references provided herein. Therefore, because Lu et al., through Wu et al., teach that covalent

coupling may alter DNA expression, and Lu et al. uses a non-covalent means as a result of that teaching, Lu et al. teaches away from the instant invention.

That Lu et al. teach a means of non-covalent coupling between the carrier, asialoglycoprotein, with an oligonucleotide, and in fact teaches away from the use of a covalent means of coupling oligonucletoides to a carrier, strongly suggests that there is no desireability to combine the references for one of ordinary skill in the art. The Examiner has used "impermissible hindsight vision" to combine the references, and therefore fails to prove a prima facie case of obviousness against the invention.

Furthermore, because Lu et al. teach a means of non-covalent interaction, as opposed to covalent coupling used in the instant application, the combination of the cited references teach that there would not be a reasonable expectation of success for the invention. One of ordinary skill in the art, with the knowledge that a covalent means of coupling the carrier to the oligonucleotide would be a damaging interaction and would not combine the art within the Nagy et al. reference. Nagy et al teaches away from Lu et al., which teaches a somatostatin molecule covalently coupled to its active agent. One of ordinary skill in the art would not have a reasonable expectation of success for the combination of the two references because Lu et al. teach that covalent coupling of oligonucleotides to a carrier would be damaging..

Adding Taylor et al. does not cure the deficiencies of Lu et al. and Nagy et al. Neither Taylor et al. nor Nagy et al. teach that covalently coupling of the antisense oligonucleotides, contrary to the teachings of Lu et al., are acceptable. Moreover, neither Taylor et al. nor Nagy et al. teach or suggest the combination of antisense oligonucleotides covalently coupled to somatostatin as a means of targeting antisense oligonucleotides to cancer cells expressing somatostatin receptors. Applicants again respectfully submit that the Examiner is using impermissible hindsight in order to come to the incorrect conclusion that the combination of the prior art references render obvious the claimed invention.

Therefore, Nagy et al., in combination with Lu et al., and even in light of Taylor et al., do not teach all of the elements disclosed within the instant application. In addition, the combination of Nagy et al., Lu et al. and Taylor et al. would not overcome the standard necessary for showing a reasonable expectation of success. The 35 U.S.C. § 103(a) rejection to Claims 1-3 should be withdrawn.

35 U.S.C. § 103(a) Rejection – Claims 1-13, 15 and 16

Claims 1-13, 15 and 16 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the combination of references of Nagy et al., in view of Lu et al., Taylor et al., Anderson et al., Khan et al., Godard et al. and Ma et al. Claims 6 and 16 have been cancelled, rendering moot the rejection to these claims. The remaining rejection to the claims are overcome in part in view of the amendments and in part in view of the remarks below.

The Examiner asserts that it would have been allegedly obvious for one of ordinary skill in the art to substitute either the bcl-2 antisense conjugate of Ma et al. or the antisense compound of Lu et al. for the cytotoxic compound of the somatostatin analog conjugates as taught by Nagy et al. The Examiner further asserts that it would have been allegedly obvious to one of ordinary skill in the art to substitute the highly bioactive somatostatin analogs of Anderson et al. in place of the analogs of Nagy et la. Furthermore, the Examiner asserts that it would have been allegedly obvious to one of ordinary skill in the art to incorporate the nuclease resistance modifications and targeting features of Taylor et al., Khan et al. and Godard et al. into such conjugates.

Applicants respectfully submit that the same arguments above against the obviousness rejection to Claims 1-3 in view of Lu et al., Nagy et al., and Taylor et al., apply to this instant rejection. The combination of Lu et al., Nagy et al. and Taylor et al. do not disclose all of the elements of the claimed invention of somatostatin covalently coupled to an oligonucleotide. Adding Anderson, Ma et al., Khan et al., or Godard et al. would not cure the deficiencies of the combination of Lu et al., Nagy et al. and Taylor et al. The combination of references, therefore, do not provide a prima facie case of obviousness against the claimed invention.

Moreover, the combination of Lu et al., Nagy et al. and Taylor et al. is improper in light of the lack of teaching or suggestion of a desireability to combine the element of a somatostatin carrier peptide-hormone molecule with an antisense oligonucleotide active agent. In fact, Lu et al. teach away from the use of a covalent coupling system, as the instant invention claims, by teaching that such a system may "alter the DNA and preclude proper gene expression." *See* Wu et al. (1997) *supra*, and comments above.

Adding Anderson, Ma et al., Khan et al., or Godard et al. would not cure the deficiencies of the improper combination of the Lu et al., Nagy et al. and Taylor et al. prior art references. The 35 U.S.C. § 103(a) rejection to claims 1-5, 7-13 and 15 should be withdrawn.

CONCLUSION

Applicants believe that the application is now in good and proper condition for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 463-8181.

Respectfully submitted,

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